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# Oral Contraceptive Pill Use is Associated With Localized Decreases in Cortical Thickness

**Nicole Petersen,[1,2]* Alexandra Touroutoglou,[3,4,5] Joseph M. Andreano,[4,5] and Larry Cahill[2]**

[1]*Department of Psychiatry and Biobehavioral Sciences, Semel Institute, University of California, Los Angeles, California*
[2]*Department of Neurobiology and Behavior, Bonney Research Laboratory, University of California, Irvine, California*
[3]*Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Massachusetts*
[4]*Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Massachusetts*
[5]*Psychiatric Neuroimaging Division, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Massachusetts*

**Abstract:** Oral contraceptive pills (OCs), which are used to prevent pregnancy by the majority of women in the United States, contain steroid hormones that may affect the brain's structure and function. In this investigation, we tested the hypothesis that OC use is associated with differences in brain structure using a hypothesis-driven, surface-based approach. In 90 women, (44 OC users, 46 naturally-cycling women), we compared the cortical thickness of brain regions that participate in the salience network and the default mode network, as well as the volume of subcortical regions in these networks. We found that OC use was associated with significantly lower cortical thickness measurements in the lateral orbitofrontal cortex and the posterior cingulate cortex. These regions are believed to be important for responding to rewards and evaluating internal states/incoming stimuli, respectively. Further investigations are needed to determine if cortical thinning in these regions are associated with behavioral changes, and also to identify whether OC use is causally or only indirectly related to these changes in brain morphology. *Hum Brain Mapp 36:2644–2654, 2015.* 

**Key words:** cortical thickness; hormonal contraception; morphometric analysis; neuroendocrinology

## INTRODUCTION

Oral contraceptive pills (OCs) are used by the majority of women in the United States for at least one period of time during their reproductive years (CDC), and are approved by the Food and Drug Administration for pediatric use after the onset of menarche [FDA, 2004]. Ample evidence has shown that brain development continues well past the onset of menarche [Giedd et al., 1999; Paus, 2005; Sowell et al., 1999], and that some features of adolescent brain development differ between male and female brains [De Bellis et al., 2001]. This is likely attributable in

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*Correspondence to: Nicole Petersen; Westwood Plaza, C8–539, Los Angeles, CA 90095. E-mail: npetersen@ucla.edu

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part to the role of ovarian steroid hormones, which have been shown to participate in the development of the brain in rodents [Bethea et al., 2002] through both "genomic" and "nongenomic" mechanisms—that is, through long-lasting, delayed onset effects on gene expression and through rapid activity that does not require gene expression [McEwen and Alves, 1999]. Ample evidence (mostly from the rodent literature) has demonstrated that adult brains undergo ongoing plastic changes, including fluctuations in the density of dendritic spines in the hypothalamus and hippocampus that are acutely sensitive to estrogen and progesterone levels [McEwen, 2002; McEwen and Woolley, 1994].

Ovarian steroid hormones, in particular 17β-estradiol (estradiol) and progesterone, are characterized by and best known for their important roles in reproduction and brain function related to reproduction. Unsurprisingly, receptors for both hormones are found in high concentration in the hypothalamus, which has a well-documented role in sexual behaviors and functioning [Law and Meagher, 1958; Singer, 1968]. However, receptors for these hormones are not restricted to brain regions associated with sex and sexual behavior. The highest concentrations of estradiol receptors outside of the hypothalamus have been found in the substantia nigra, followed by the prefrontal cortex [PFC; Bixo et al., 1995], and the highest concentrations of progesterone receptors outside of the hypothalamus have been found in the amygdala and cerebellum [Bixo et al., 1997].

Previous morphometric analyses have already shown that changes in hormone levels are associated with changes in brain structure. In a within-subjects design, gray matter increased in the right anterior hippocampus and decreased in the right dorsal basal ganglia during the high ovarian hormone phase preceding ovulation [Protopopescu et al., 2008]. Other investigations have shown that estradiol correlates negatively with prefrontal, parietal, and middle temporal regional volumes, correlates positively with the volume of middle frontal, inferior temporal, and middle occipital regions in adults [Peper et al., 2009], and correlates positively with parahippocampal gray matter volumes in adolescents [Neufang et al., 2009].

OCs contain synthetic estradiol and progesterone analogs that decrease levels of endogenous estrogens [Kjeld et al., 1976] and progesterone [Rabe et al., 1997] by binding to estrogen and progesterone receptors. Previous investigations have found effects of hormonal contraceptive use on brain structure. Differences have been observed in white matter tracts (De Bondt et al., 2013a) and in cortical gray matter [Pletzer et al., 2010], however, in the Pletzer et al. investigation, the specific contraceptive type was not noted, and a second study failed to find a significant effect in similar brain regions (De Bondt et al., 2013b). Both of these studies used voxel-based morphometry to perform a data-driven comparison of the brains of hormonal contraceptive users to naturally-cycling women. It can be difficult to achieve adequate statistical power to detect structural brain differences using this method without very large sample sizes due to the large quantity of data points collected and analyzed.

Many of the regions found to vary in size between naturally-cycling women and OC users in these previous studies belong to common networks as defined by intrinsic functional connectivity [Yeo et al., 2011]. In particular, Pletzer et al. found greater volumes in hormonal contraceptive users in the midtemporal gyrus, hippocampus, parahippocampal gyrus, and PFC, all of which are nodes in the default mode network [Buckner et al., 2008]. This network is believed to be involved in the processing of internally generated stimuli such as thoughts and memories [Buckner et al., 2008], and the functional connectivity between its constituent structures predicts individual differences in memory ability, whether measured at encoding [Dickerson et al., 2007], or at rest [Wang et al., 2010]. Similarly, Pletzer et al. found the largest effect of hormonal contraceptive use on volume in the anterior cingulate cortex, a structure found by de Bondt et al. to significantly correlate in size with estrogen levels [De Bondt et al., 2013b; Pletzer et al., 2010]. The anterior cingulate cortex is a central node in the salience network, a group of structures believed to be involved in the processing of affective information [Barrett and Satpute, 2013], whose resting connectivity predicts individual differences in subjective ratings of affective intensity [Hermans et al., 2011; Seeley et al., 2007; Touroutoglou et al., 2012].

Consistent with these observations, studies of functional activation during encoding of affective and neutral stimuli have shown that activity within the salience and default mode networks differs significantly between menstrual phases [Toffoletto et al., 2014]. In the salience network, encoding activity in both the anterior cingulate cortex (ACC) and amygdala (another key salience network node) is significantly greater during the luteal phase compared with the follicular phase [Amin et al., 2006; Andreano and Cahill, 2010; Gingnell et al., 2012; Ossewaarde et al., 2010]. Similarly, activity in the default mode network also varies in women depending on hormonal status. Encoding activity in the hippocampus is greater during the high-estrogen late-follicular phase compared with midcycle, [Goldstein et al., 2005] and during working and spatial memory tasks, late follicular activity is greater in the midtemporal gyrus and precuneus [Bannbers et al., 2012; Joseph et al., 2012; Weis et al., 2011]. Evidence from both structural and functional imaging, therefore, indicates that the default and salience networks are particularly sensitive to variation in ovarian hormone levels. Thus, it seems likely that the use of OCs could influence brain structure, just as endogenous hormone fluctuations do, and we hypothesized that OC use may be associated with changes in the thickness and volume of brain regions populated by estradiol and progesterone receptors.

To test this, we performed a hypothesis-driven analysis to compare the volume and thickness of specific regions of interest within the default and salience brain networks of oral contraceptive users to those of naturally-cycling women. Our objective was to test the hypothesis that

women who use OCs have significant differences in the volume and thickness of specific brain regions associated with affective processing that may be related to OC use, and may be related to behavioral changes associated with OC use, such as altered affective control.

## MATERIALS AND METHODS

The structural images for this experiment were collected as part of a previously-published investigation [Petersen et al., 2014]. The participant screening, selection, inclusion/exclusion criteria, and consent process to collect the data reported here is identical to that previously reported. It will be summarized briefly, and then the methods that diverge from Petersen et al. [2014] will be described in detail.

### Participants

Four groups of participants were recruited for this study: naturally-cycling ("NC") women in the follicular phase of the menstrual cycle (days 2–6, "follicular"); naturally-cycling women in the luteal phase of the menstrual cycle (days 18–24, "luteal"); oral contraceptive ("OC") users during the inactive pill phase ("inactive OC"); and oral contraceptive users during the active pill phase ("active OC"). Because combined (estradiol and progestin-containing) OCs include 21–24 days of hormone-containing pills, and 4–7 days of inactive pills with no hormones, we were able to separately analyze data from women during the active and inactive pill phases to provide a rough estimate of the time course of the effects we measured. Only participants using monophasic, combined oral contraceptives (COCPs) with 28-day cycles were included. Each participant was screened by telephone to ensure no history of psychiatric, neurological, or endocrine disorders, and to ascertain Magnetic Resonance Imaging (MRI) safety status. The experiment was approved by the UC Irvine IRB and written, informed consent was given by all participants before inclusion in the study.

Data from three participants were not included in the analysis due to errors in data acquisition. One outlier was excluded from group analysis once her morphometry analysis was complete due to volume and thickness measurements >3SDs from the mean. Two participants were consented and scanned, but at the time of scanning, reported menstrual cycle onset dates that were inconsistent with previous reports during telephone screening. Due to this inconsistency, these participants were excluded from all analysis. Thus, 90 participants were included in the final analysis: 44 OC users (22 during the inactive pill week, and 22 using active pills) and 46 NC women (21 follicular, 25 luteal).

### Salivary Hormone Collection and Analysis

Two saliva samples were collected from participants to assay salivary estradiol and progesterone levels as previously described in Petersen et al. [2014]. The same salivary hormone data was used here, with the excluded participants removed from analysis.

**TABLE I. Salivary estradiol and progesterone concentrations are given for each group**

| | Salivary estradiol concentration (pg/mL) ±SD | Salivary progesterone concentration (pg/mL) ±SD |
|---|---|---|
| NC, Follicular | 3.33 ± 0.85 | 99.7 ± 53.4† |
| NC, Luteal | 3.59 ± 0.26 | 137.9 ± 83.1 |
| OC, Inactive | 2.77 ± 1.15* | 57.6 ± 45.2* |
| OC, Active | 2.72 ± 1.39* | 73.2 ± 58.1* |

*Significant difference from luteal group at $P < 0.05$.
†Significant difference between follicular and inactive OC groups at $P < 0.05$.

### MRI Image Acquisition

MRIs were performed at the University of California, Irvine Research Imaging Center's 3-Tesla Philips MRI (Eindhoven, The Netherlands). Structural images were acquired over 449 s in 160 slices with TR = 8.106, FOV = 240 × 240 × 160, resolution = 240 × 240, TE = 3.73 s, flip angle = 8°.

### Region of Interest Selection

Based on our hypotheses, we selected regions within the salience and default mode networks (see Tables I and II for a list of regions of interest). For cortical thickness and volumetric measures of regions within the default mode network [Andrews-Hanna et al., 2010; Buckner et al., 2008], we selected the posterior cingulate cortex, inferior parietal region, medial temporal cortex as well as the parahippocampal cortex, and hippocampus. For cortical thickness and volumetric measures of regions within the salience network [Seeley et al., 2007; Touroutoglou et al., 2012, 2014], we selected the insula, anterior cingulate cortex, supramarginal gyrus, and orbitofrontal cortex as well as the amygdala.

### Structural MRI Analysis

The quantitative morphometric analysis of T1-weighted magnetization-prepared rapid acquisition with gradient echo MRI data was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu;).

#### *Subcortical MRI segmentation methods*

For subcortical segmentation, this method uses a manually labeled atlas dataset from 40 individuals to automatically segment and assign neuroanatomic Region of Interest (ROI) labels to 37 different brain structures based on

**TABLE II. In the salience network, NC women had significantly thicker bilateral medial and lateral orbitofrontal cortex, left caudal anterior cingulate cortex, and left insula**

| | Left hemisphere | | | Right hemisphere | | |
|---|---|---|---|---|---|---|
| Structure | *F*-statistic | *P*-value | Cohen's *d* | *F*-statistic | *P*-value | Cohen's *d* |
| Caudal anterior cingulate thickness | 4.6995 | **0.0329*** | **0.47** | 0.0246 | 0.8757 | |
| Rostral anterior cingulate cortex thickness | 0.5975 | 0.4416 | | 1.3629 | 0.2462 | |
| Insula thickness | 5.6809 | **0.0193*** | **0.52** | .6092 | .4372 | |
| Lateral orbitofrontal cortex thickness | 15.1241 | **0.0002***** | **0.80** | 9.9721 | **0.0022**** | **0.71** |
| Medial orbitofrontal cortex thickness | 4.359 | **0.0399*** | **0.45** | 6.9076 | **0.0101*** | **0.60** |
| Supramarginal cortex thickness | 1.1697 | 0.2825 | | 1.5631 | 0.2146 | |
| Amygdala volume (adjusted) | 1.5641 | 0.2144 | | 0.0962 | 0.7571 | |

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

probabilistic estimations. Using Bayesian statistics, the probability of the presence of a particular neuroanatomic structure at a particular location is estimated given the image intensity, the likelihood that a particular tissue class would be present at a given location, and the probability of a particular anatomic structure given the tissue types within a local area. This automated segmentation procedure has been widely used in volumetric studies and was shown to be comparable in accuracy to that of manual labeling [Fischl et al., 2002]. In this study, the anatomic dataset was processed using the fully automated algorithm and then the subcortical segmentations of each subcortical ROI were manually verified. The subcortical ROIs on which we focused in this study included the amygdala, brainstem, and hippocampus; for each structure, the volumetric measurement was obtained from the FreeSurfer output file and divided by total intracranial volume.

### *Cortical parcellation and estimation of cortical thickness*

After spatial and intensity normalization and skull stripping, the resulting volume was then used to segment cerebral white matter [Dale et al., 1999] and locate the gray/white matter boundary. Using FreeSurfer's algorithms (http://surfer.nmr.mgh.harvard.edu), defects in the surface topology were corrected [Fischl et al., 2001] and the gray/white boundary was deformed outward using an algorithm designed to obtain an explicit representation of the pial surface [Fischl and Dale, 2000]. For the purposes of comparing cortical thickness measures across subjects, it is necessary to establish a common surface-based coordinate system. To achieve this, a spherical averaging method was used to normalize and align cortical folding patterns across subjects by morphing and registering each subject's reconstructed brain to an average spherical surface representation. Each subject's surface was then divided into cortical ROIs by labeling each of approximately 160,000 points per hemisphere based on (1) prior probability of that label matching a location on an atlas derived from a manually-parcellated training set, (2) local curvature information, and (3) information about the adjacent labels and folding patterns.

We obtained cortical thickness measures for 12 ROIs per hemisphere (see Tables II and III for a list of ROIs) derived mostly from previously developed parcellation schemes [Desikan et al., 2006].

## RESULTS

### Salivary Hormone Levels

Salivary hormone differences between the NC and OC groups were tested by one-way Analysis of Variance (ANOVA). NC women had significantly higher salivary estrogen compared with OC women, $F_{(1,88)} = 6.97$, $P = 0.0098$. NC women also had significantly higher salivary progesterone compared with OC women, $F_{(1,88)} = 16.84$, $P < 0.0001$.

Subgroup analysis showed that luteal women had significantly elevated salivary estrogen compared with active pill users ($P = 0.0265$) and compared with inactive pill users ($P = 0.0378$), but not follicular women ($P = 0.1271$). Luteal women also had significantly elevated salivary progesterone compared with active pill users ($P = 0.0007$), inactive pill users ($P < 0.0001$), and follicular women ($P = 0.0418$). Follicular women had significantly higher salivary progesterone levels than inactive pill users ($P = 0.0302$).

### Regional Volume and Thickness Differences

#### *Planned comparisons*

Total intracranial volumes were compared between groups by one-way ANOVA. NC women were found to have higher overall brain volume, $F_{(1,88)} = 4.82$, $P = 0.031$.

Once the volume of each subcortical brain region was calculated, subcortical volumes were corrected for total brain volume (regional volume/total intracranial volume). Next, the volume of each subcortical region, and the thickness of each cortical region, participating in the two

**TABLE III. In the default mode network, the left posterior cingulate cortex was significantly thinner in OC users compared with NC women**

| | Left hemisphere | | | Right hemisphere | | |
|---|---|---|---|---|---|---|
| Structure | *F*-statistic | *P*-value | Cohen's *d* | *F*-statistic | *P*-value | Cohen's *d* |
| Middle temporal cortex thickness | 2.9673 | 0.0885 | | 3.0458 | 0.0845 | |
| Parahippocampal cortex thickness | 0.5752 | 0.4503 | | 0.2549 | 0.6150 | |
| Posterior cingulate cortex thickness | 10.7934 | **0.0015**** | **0.68** | 1.2516 | 0.2663 | |
| Inferior parietal cortex thickness | 1.7941 | 0.1839 | | 3.0756 | 0.0830 | |
| Hippocampal volume (adjusted) | 0.2045 | 0.6522 | | 0.2486 | 0.6193 | |

*$P < 0.05$.

networks chosen (the salience network and the default mode network) was compared between groups. One-way ANOVA was used to test the hypothesis that NC and OC users differed in the regions of interest selected.

The results of all comparisons in the salience network are shown in detail in Table II, and results of comparisons in the default mode network in Table III. In every comparison where a significant result emerged, the direction of the relationship was the same: NC women had significantly larger brain regions than did OC users.

In the salience network, the left caudal anterior cingulate, left insula, and left and right lateral orbitofrontal cortex ROIs were significantly thinner in OC users compared with NC women.

In the default mode network, the posterior cingulate cortex was significantly thinner in OC users compared with NC women.

### *Multiple comparison correction*

Although we selected a priori regions of interest to avoid the problems introduced by the number of comparisons involved in whole-brain and voxelwise analyses, the total number of planned comparisons (24) was still quite high. A formal Bonferroni correction, therefore, reduces our alpha-level to 0.002 (0.05/24). The regions that survive this threshold are the left lateral orbitofrontal cortex comparison in the salience network and the left posterior cingulate cortex in the default mode network.

Using the false discovery rate, which is less conservative but also less susceptible to rejecting true positives [Glickman et al., 2014], the same regions survive multiple comparison correction, as does the right lateral orbitofrontal cortex comparison.

### *Post hoc subgroup comparisons*

Because the two groups compared with one another each contained hormonally distinct subgroups, we performed post hoc *t*-tests to determine whether any of the four subgroups (follicular, luteal, active OC, inactive OC) differed significantly in the regions where volume or thickness differences had been detected using an uncorrected significance threshold of 0.05: the left caudal anterior cingulate, left insula, left and right lateral orbitofrontal cortices, left and right medial orbitofrontal cortices, and posterior cingulate cortex.

In the left caudal anterior cingulate, two-way *t*-tests showed that the follicular group had significantly thicker cortex compared with the active OC group, $P = 0.0026$; the luteal group also had significantly thicker cortex compared with the active OC group, $P = 0.0313$, and the inactive OC group had significantly thicker cortex compared with the active OC group, $P = 0.0378$ (Fig. 1).

In the left insula, the cortex in the follicular group was significantly thicker than that in the left insula of inactive OC users, $P = 0.0212$ (Fig. 2).

In the left lateral orbitofrontal cortex, the follicular group had significantly thicker cortex compared with inactive OC users ($P = 0.0003$) or active OC users ($P = 0.0428$), and the luteal group's cortex was significantly thicker than inactive OC users, $P = 0.0007$ (Fig. 3).

In the right lateral orbitofrontal cortex, the follicular group had significantly thicker cortex compared with active OC users ($P = 0.001$) or inactive OC users ($P = 0.002$) or luteal women ($P = 0.0434$; Fig. 4).

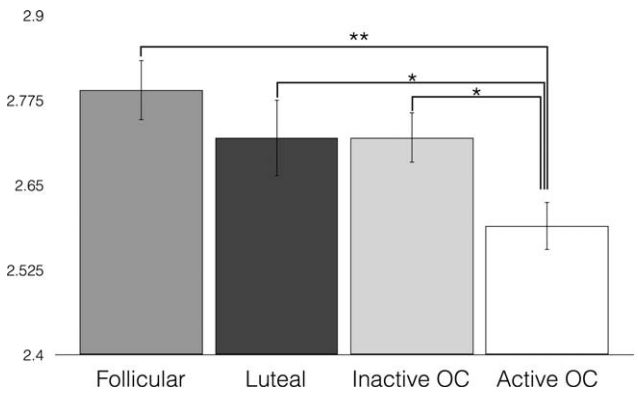


**Figure 1.**
The follicular, luteal, and inactive OC groups all had significant thicker left caudal anterior cingulate cortices. Bars denote mean thickness ±SEM. **$P < 0.01$, *$P < 0.05$.

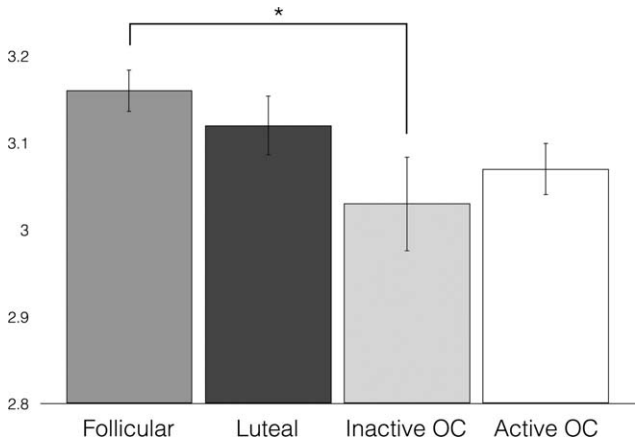


**Figure 2.**
The follicular group had a significantly thicker left insula compared with the inactive OC group. Bars denote mean thickness ±SEM. *$P < 0.05$.

In the left posterior cingulate, follicular ($P = 0.0011$) and luteal ($P = 0.0033$) women had significantly thicker cortex compared with active OC users (Fig. 5).

In the left medial orbitofrontal cortex, the follicular group had significantly thicker cortex compared with active OC users, $P = 0.0114$ (Fig. 6).

In the right medial orbitofrontal cortex, the follicular group had significantly thicker cortex than the inactive OC users ($P = 0.0049$) or the active OC users ($P = 0.0116$; Fig. 7).

## Hormone Correlations

We tested the hypothesis that a linear relationship may exist between brain morphometry and one of the two

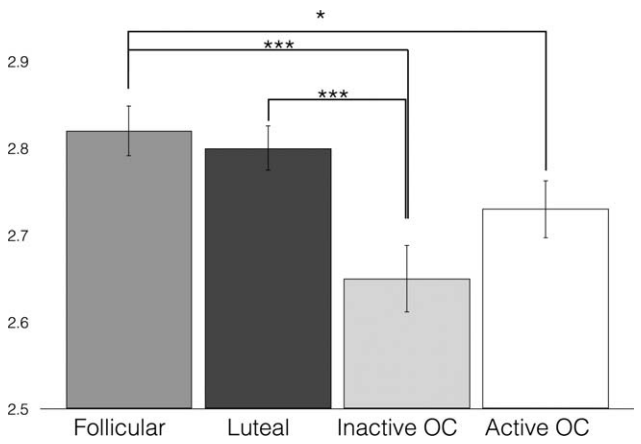


**Figure 3.**
The inactive OC group had a significantly thinner left lateral orbitofrontal cortex compared with either naturally-cycling group. The active OC group also had a significantly thinner cortex here compared with the follicular group only. Bars denote mean thickness ±SEM. ***$P < 0.001$, *$P < 0.05$.

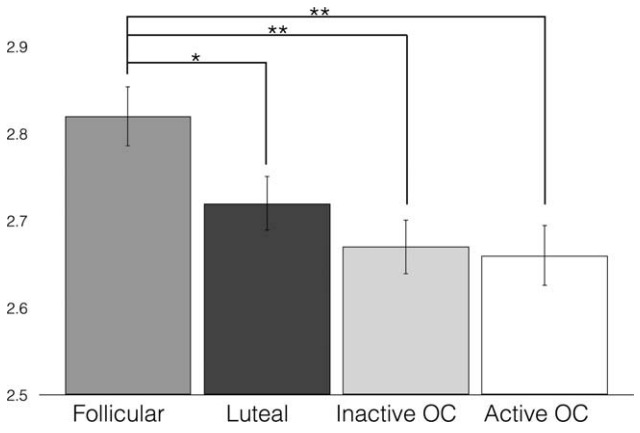


**Figure 4.**
Each group's right lateral orbitofrontal cortex was significantly thinner than the follicular group's. Bars denote mean thickness ±SEM. **$P < 0.01$, *$P < 0.05$.

major sex hormones we measured, estradiol and progesterone, by performing linear correlations between these hormones levels as measured in saliva and each brain region that differed significantly at the uncorrected threshold of 0.05. At this uncorrected threshold, salivary progesterone correlates positively with the thickness of the left insula, $r(87) = 0.22$, $P = 0.04$, and salivary estradiol correlates positively with the thickness of the left lateral orbitofrontal cortex, $r(87) = 0.23$, $P = 0.03$. However, given the number of comparisons and the low degree of correlation, it may be more appropriate to interpret these hormone correlations as null findings.

As an exploratory analysis, we repeated these correlations in each of six subgroups: NC, OC, follicular, luteal, inactive OC, and active OC. All correlations are reported in Supporting Information, and are summarized next. As previously discussed, given the large number of comparisons performed (2 hormones × 6 groups × 7 brain regions = 84), the following results should be considered

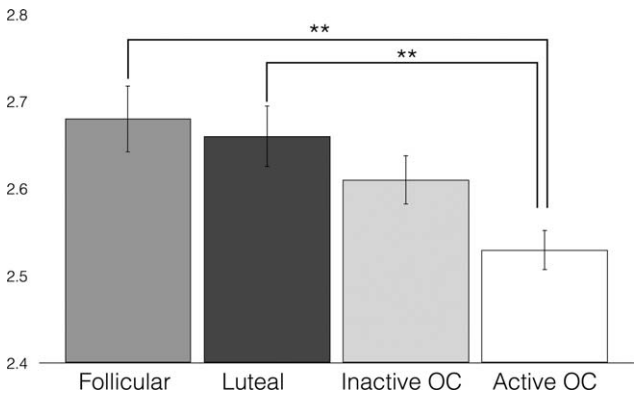


**Figure 5.**
The left posterior cingulate cortex was significantly thinner in active OC users compared with either naturally-cycling group.

exploratory rather than conclusive, and would not survive correction for multiple comparisons ($\alpha = 0.0006$).

In NC women, the significant correlation between salivary estradiol and left lateral orbitofrontal thickness was retained and strengthened, $r(45) = 0.43$, $P = 0.0025$. By contrast, in OC users, estrogen did not correlate with thickness in this region, $r(42) = -0.12$, $P = 0.45$. These two correlations differ significantly from one another, $z = 2.63$, $P = 0.0085$. Further subdividing the NC group into follicular and luteal women indicated a significant relationship between estradiol and cortical thickness here only in luteal, $r(22) = 0.54$, $P = 0.007$, but not follicular women, $r(19) = 0.35$, $P = 0.12$.

Within the OC group only, a significant negative relationship was found between salivary estradiol and the thickness of the right medial orbitofrontal cortex, $r(42) = -0.44$, $P = 0.003$. This relationship was strengthened in the active OC group, $r(20) = -0.57$, $P = 0.0052$, and was marginally significant in the inactive OC group, $r(20) = -0.41$, $P = 0.0553$. In the opposite hemisphere, estradiol again negatively correlated with the thickness of the left medial orbitofrontal cortex in the OC group, $r(20) = -0.46$, $P = 0.032$, but not in the inactive OC group, $r(20) = -0.05$, $P = 0.83$.

The relationship between progesterone and the left insula was not retained in any subgroup analysis. However, progesterone did have a marginally significant positive correlation with the thickness of the right lateral orbitofrontal cortex in the inactive OC group only, $r(20) = 0.42$, $P = 0.05$.

We also attempted to replicate the finding of De Bondt et al. (2013b) that estradiol correlates negatively with the volume of the right ACC in luteal women. A linear correlation showed no significant relationship between the two variables in the caudal ACC $r(22) = -0.23$, $P = 0.28$ or the rostral ACC, $r(22) = 0.13$, $P = 0.53$, or with a combined ROI of caudal ACC + rostral ACC, $r(22) = 0.07$, $P = 0.73$. However, a marginally significant negative correlation was found between salivary estradiol and left caudal ACC thickness in follicular women, $r(19) = -0.44$, $r = 0.0448$.

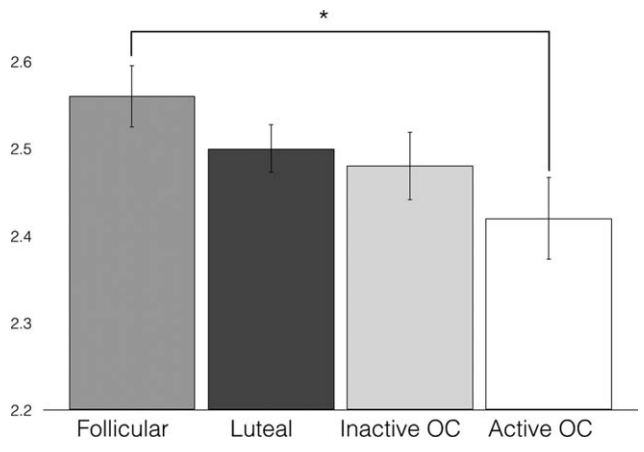


**Figure 6.**
The left medial orbitofrontal cortex was significantly thinner in active OC users compared with follicular women.

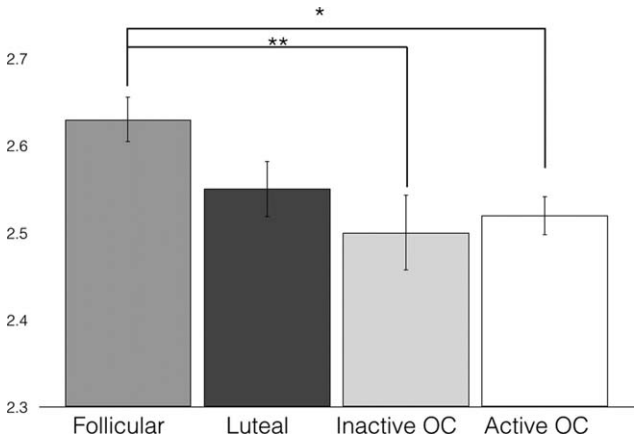


**Figure 7.**
The right medial orbitofrontal cortex was significantly thinner in both inactive and active OC users compared with follicular women.

Based on evidence that the ratio of estrogen to progesterone (E:P) may have a different influence on the brain than either hormone alone [e.g., Beckham et al., 1992], we also tested the relationship between this ratio and the seven regions of cortical thickness described in Table IV. No significant relationships were found between E:P and the thickness of any region, all $P$s $> 0.47$.

## DISCUSSION

Here, we found that some, but not all, brain regions that participate in the salience network and the default mode network were smaller in women using OCs compared with naturally-cycling women. Larger cortical thickness values in NC women were found in the left caudal anterior cingulate, left insula, bilateral lateral orbitofrontal cortex, bilateral medial orbitofrontal cortex, and left posterior cingulate cortex at an uncorrected alpha-level of 0.05. The bilateral lateral orbitofrontal cortex and posterior cingulate cortex comparisons survive multiple correction using the false discovery rate, and the left lateral orbitofrontal cortex and posterior cingulate cortex comparisons survive Bonferroni correction.

Post hoc analysis to determine which subgroup (follicular, luteal, active OC, inactive OC) drove these effects revealed the general pattern that thicker cortical regions in the NC group tended to be driven by the thickness of follicular, rather than luteal women's cortices. In each region, where a significant difference was detected, the follicular group differed significantly from at least one of the two OC groups. In the left lateral orbitofrontal cortex and left posterior cingulate cortex, the luteal group also differed

**TABLE IV. Salivary progesterone correlates weakly with the thickness of the left insula, and salivary estrogen correlates weakly with the thickness of the left lateral orbitofrontal cortex. Both are significant at an alpha-level of 0.05, but do not survive multiple comparison correction**

| Cortical structure thickness | Progesterone $R^2$ | Progesterone $P$-value | Estrogen $R^2$ | Estrogen $P$-value |
|---|---|---|---|---|
| Left caudal ACC | 0.00 | 0.94 | 0.00 | 0.81 |
| Left insula | **0.05** | **0.04*** | 0.00 | 0.79 |
| Left lateral orbitofrontal | 0.04 | 0.05 | **0.05** | **0.03*** |
| Right lateral orbitofrontal | 0.02 | 0.21 | 0.01 | 0.37 |
| Left medial orbitofrontal | 0.01 | 0.31 | 0.00 | 0.92 |
| Right medial orbitofrontal | 0.01 | 0.32 | 0.00 | 0.68 |
| Left posterior cingulate | 0.02 | 0.16 | 0.02 | 0.17 |

*$P < 0.05$.

from one of the two OC groups. One menstrual phase effect was also found in the right lateral orbitofrontal cortex, where again, follicular women showed the thickest cortex, this time differing significantly from the luteal women. In none of the regions analyzed was the cortex thicker in luteal women or in either OC group.

Because post hoc testing revealed that the observed effects were driven by differences between OC users and follicular women (as opposed to differences between OC users and luteal women), this specific pattern of differences suggests that at least some of the effects reported here may be attributable to the synthetic hormones in OCs, rather than attributable to decreases in endogenous hormone levels. If the lowered endogenous hormone levels observed in the OC group were responsible for the observed changes in brain morphometry, then the largest difference should have been found between OC users and luteal women, in whom hormone levels were highest, rather than between OC users and follicular women, in whom hormone levels were intermediate. Further, because differences were observed between NC women and OC users during the inactive pill week, this suggests that OCs' influence on morphology is not an acute effect but persists for at least the one-week duration of inactive pill use. One exception to this was in the left ACC, where the active and inactive OC groups differed significantly from one another, suggesting an acute effect of OCs on this brain region. Future studies will be needed to assess whether the effects reported here that did persist during the inactive OC week last for weeks, months, years, or permanently.

Despite this evidence that synthetic hormones may be influencing cortical thickness, other findings in this experiment implicate endogenous hormones, in particular, estrogen. We found a significant, positive correlation between estradiol levels and left lateral orbitofrontal cortex thickness, although we consider this finding to be exploratory/preliminary due to the high number of correlations performed. The relationship between estradiol and left lateral orbitofrontal cortex (OFC) thickness was found in the whole sample, but subgroup analysis revealed that this was driven entirely by the correlation in NC women. In OC women, estradiol no longer predicts OFC cortical thickness.

Some evidence indicates that estrogen is a plausible modulator of brain structure in the PFC. Although studies in humans have been limited, postmortem studies have shown that the PFC has a relatively high density of estrogen receptors in humans; only the hypothalamus and substantia nigra are more densely populated [Bixo et al., 1995]. Estrogen receptor mRNA is also highly expressed throughout the PFC in both humans and monkeys [Perlman et al., 2005]. This roughly parallels findings from rodent literature that show that estrogen receptors populate most regions of the brain, with especially high densities in the hypothalamus and rat isocortex [Shugrue et al., 1997].

The lateral OFC cortex was the region with the largest effect of hormone levels, and also the most significant difference between NC women and OC users. The lateral OFC is believed to be involved in cognitive control of behavior, including response inhibition to stimuli with changing reward value [Elliott et al., 2000], and effortful emotion regulation using cognitive reappraisal [Goldin et al., 2008] or suppression of emotions [Ochsner et al., 2004]. The lateral OFC responds specifically to punishing (as opposed to rewarding) outcomes [O'Doherty et al., 2001].

Cortical thickness differences also survived multiple comparison correction in the posterior cingulate cortex. The posterior cingulate cortex (PCC) participates in the default mode network [Fransson and Marrelec, 2008] and it has been posited that the PCC is responsible for evaluating sensory stimuli, the internal state [Vogt et al., 1992], and incoming emotional information [Maddock et al., 2003]. In no group, did we see even preliminary evidence that endogenous hormone levels correlated with PCC thickness, suggesting that endogenous estrogen or progesterone levels do not mediate effects of OCs on PCC structure.

Two previous studies have documented effects of hormonal contraceptives on brain structure. Pletzer et al. [2010] reported increased regional gray matter volumes in hormonal contraceptive users compared with naturally-

cycling women in the PFC, precentral gyrus, postcentral gyrus, parahippocampal cortex, fusiform gyrus, and temporal cortex using voxel-based morphometry. Our findings were not consistent with this, perhaps due to differences in the study population, differences in the analysis techniques, or both. Pletzer et al. [2010] included participants using any form of hormonal contraceptives; we included only women using COCPs. It may be the case that other forms of hormonal contraceptives, especially those containing progestin only and no synthetic estrogen, have a very different influence on brain morphometry than do COCPs. Further, Pletzer et al. used whole brain voxel-based morphometry whereas we used a hypothesis-driven ROI approach.

We also partially failed to replicate the findings of De Bondt et al. (2013b) that estradiol correlates negatively with the volume of the ACC in luteal women. We found no significant relationship between estradiol and right ACC thickness in our slightly larger group of luteal women ($N = 25$ compared with 15). However, we did find a similar negative relationship between estradiol and left caudal ACC thickness in follicular women. It is possible that a voxel-based approach in our dataset would have uncovered a relationship between estradiol and ACC volume in luteal women in some subset of ACC voxels that was not present in the rostral or caudal divisions we tested. The lack of consistency between our findings and previous investigations highlight the importance of replication, and the need for further studies in this field.

This study has a number of important limitations that must be acknowledged. Primarily, for ethical and practical reasons, we used a quasiexperimental design using women who have chosen to use OCs for at least 3 months without electing to discontinue, rather than using a randomized design with a placebo control. It is possible that the participants who chose to begin OC use differ systematically in some way compared with participants who did not, although our participants did not differ in basic demographic characteristics, and other investigations have shown that hormonal contraceptive users do not differ from NC women on personality measures, SAT scores, or political orientation [Petersen et al., 2014b]. Additionally, within the naturally-cycling group, follicular and luteal women did not have significantly different estradiol levels, despite relatively conservative definitions of the follicular and luteal phases. The absence of this difference may have masked a real difference in the brain structure of luteal and follicular women that may be revealed by other investigations.

An important constraint in the interpretation of these findings is the absence of behavioral data. While we believe it is scientifically important to investigate the effects of OCs on brain structure, and these findings may inform behavioral studies, the data presented here do not and cannot provide any information regarding the effects of OC on any behavior. We speculate that, on the basis of the structural changes we observed in the lateral OFC, OCs may influence performance on tasks that involve this region, especially functions that further involve the participation of the salience and default mode networks. In particular, we speculate that it is possible that effortful emotion regulation using cognitive reappraisal or suppression, which relies on cortical control of limbic activation, may be less effective in OC users. Additionally, OCs may influence response inhibition more generally. Although this particular hypothesis has not been tested, evidence has shown that menstrual phase influences motor inhibitory control [Colzato et al., 2010] and also influences the neural response to rewarding stimuli [Dreher et al., 2007]. Future investigations are needed to determine if OC use influences emotion regulation, behavioral inhibition, or response to reward.

The group differences we observed in the PCC, a critical default mode network node, suggest that behavioral differences may also be detected between NC women and OC users in tasks that demand default mode network activation or deactivation, which may be beneficial, detrimental, or both, depending on task demands. For instance, increased default mode network connectivity has been detected in both schizophrenia and depression [Whitfield-Gabrieli and Ford, 2012], but decreased default mode activity has been associated with Alzheimer's Disease [Greicius et al., 2004]. These findings suggest that potential behavioral effects of altered PCC structure are widespread, but difficult to predict.

Behavioral differences may also be observed in behaviors that depend on network-level activity. For instance, behaviors linked to the default mode network, include remembering, considering hypothetical scenarios, and imagining future events [Buckner et al., 2008], and behaviors linked to the salience network include error monitoring [Ham et al., 2013] and engaging attentional processes when demanded [Menon and Uddin, 2010].

Importantly, given the disparity in findings in OC effects on brain structure, it is critical that these findings are replicated before strong conclusions can be drawn. Better still, a randomized, placebo-controlled, longitudinal investigation of OC use on brain structure will provide gold standard evidence of this effect. Additionally, future studies can investigate the time course of these effects. It is currently not known whether these effects appear immediately after initiating OC use, or gradually accumulate and increase over time. Further, it is not known how long these effects persist after OC discontinuation. We hope that these findings provide compelling evidence for future investigators to determine the answers to these questions.

In conclusion, using a hypothesis-driven analysis of brain morphometry, we found that the cortex in several regions is thinner in OC users compared with naturally-cycling women, and that this effect is driven primarily by differences between contraceptive users and women in the follicular phase of the menstrual cycle, when endogenous hormone levels are already quite low. This suggests that the synthetic estrogen and progestins in OCs may decrease cortical thickness bilaterally in the lateral orbitofrontal

cortex, and in the posterior cingulate cortex. Whether this is causally related to oral contraceptive use, and the functional significance of this cortical thinning, remain to be investigated.

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